IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re Application of: Friede et al.	Group Art Unit: 1648
Filed: 28 March 2001	Examiner: Z. Lucas
Serial No.: 09/819,464	Atty Reference: B45070 US1
For: Vaccines	Date: June 11, 2009

MAIL STOP APPEAL BRIEF – PATENTS
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

APPEAL BRIEF

Sir:

This Appeal Brief is filed pursuant to the "Notice of Appeal to the Board of Patent Appeals and Interferences" filed December 11, 2008.

REAL PARTY IN INTEREST

The subject application is owned by SmithKline Beecham Biologicals SA.

RELATED APPEALS AND INTERFERENCES

None.

STATUS OF CLAIMS

Claims 74-84, 94 and 95 are pending in this application. The final rejection of Claims 74-84, 94 and 95 as obvious is appealed.

The application was originally filed with claims 1-49. In response to a restriction requirement, Applicants elected method claims 47 and 48 and later added new dependent claims 50-73. Claims 1-46 and 49 were withdrawn being drawn to non-elected inventions. All the original claims were later canceled and replaced with new composition claims 74-84 and with new method claims 85-93, dependent upon the composition claims. In response to a second restriction requirement, Claims 74-84 were elected, and the non-elected method claims were withdrawn and later canceled. A new method claim, claim 96 was added and then subsequently canceled, leaving claims 74-84, 94 and 95 pending.

STATUS OF AMENDMENTS

The claims were not amended following the Final Office Action dated July 8, 2008 and Advisory Action dated December 12, 2008.

SUMMARY OF THE CLAIMED SUBJECT MATTER

The present invention concerns (claim 74) a composition comprising: 1) an antigen; 2) a saponin which is substantially pure QS21; 3) a sterol that is present in excess weight with respect to the saponin and wherein the ratio of saponin to sterol does not exceed 1:100 w/w. Basis for claim 74 is found on the specification page 4 lines 17-18 and 32 and page 10 lines 12-13. Basis for the claims is found throughout the specification generally and is laid out specifically in Applicants' March 22, 2005 Response on page 5.

GROUPING OF CLAIMS

Claims 74-84, 94 and 95 stand or fall together on the issue of obviousness in light of the prior art.

Additionally, claim 95 stands or falls on the issue of obviousness in light of the prior art and routine optimization.

GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

Claims 74-76, 78, 80, 82-84, 94 have been rejected by the Examiner under 35 U.S.C. §103 as being unpatentable over Lipford (Vaccine 12:72-80) in view of the teachings of Kensil (U.S Pat No. 5,583,112).

Claims 77, 79 and 81 have been rejected by the Examiner under 35 U.S.C. §103(a) as being unpatentable over Lipford (Vaccine 12:72-80) in view of the teachings of Kensil (5,583,112) and

further in view of Prieels et al. (WO94/00153).

Claim 95 is rejected by the Examiner under 35 U.S.C. §103(a) as being unpatentable over Lipford (Vaccine 12:72-80) in view of the teachings of Kensil (5,583,112) combined with routine optimization.

ARGUMENT

I. Ground for rejection: Claims 74-76, 78, 80, 82-84, 94 have been rejected by the Examiner under 35 U.S.C. §103 as being unpatentable over Lipford (Vaccine 12:72-80) in view of the teachings of Kensil (U.S Pat No. 5,583,112). According to the Examiner, Lipford teaches a composition comprising an antigen, Quil A and cholesterol in a saponin/sterol ratio of 1:12.5. See August 10, 2005 Office Action, page 4 first full paragraph. Kensil teaches heterogeneous compositions of saponins, like Quil A, can be separated into fractions of purified saponins, including purified QS21 (shown as QA21 in Kensil columns 5 and 6). According to the Examiner, Kensil discloses that the purified QS21 taught in the Kensil reference is an obvious substitute for Quil A in the Quil A composition of Lipford because:

(1) QS21 has adjuvant effects equal to or greater than Quil A. (August 10, 2005 Office Action, page 4 second full paragraph, citing Kensil column 6 and columns 22-23);

(2) purified saponins show adjuvant effects at lower doses than crude saponin extracts (*Id*. citing Kensil column 6 lines 30-37) and

(3) purified saponins are less toxic (hemolytic) than the Quil A extract. (*Id.* citing Kensil column 27 lines 9-22).

Claims 77, 79 and 81 have been rejected by the Examiner under 35 U.S.C. §103(a) as being unpatentable over Lipford (Vaccine 12:72-80) in view of the teachings of Kensil (5,583,112) and further in view of Prieels et al. (WO94/00153). Claims 77, 79 and 81 include the additional

limitations of lipopolysaccharide derivatives and metallic salt in the claimed composition. The additional limitations of claims 77, 79 and 81 are not disclosed in Lipford or Kensil. However, Prieels et al., discloses adjuvant compositions having lipopolysaccharide derivatives and metallic salts. (August 10, 2005 Office Action, page 6 second full paragraph.)

A. The art does not suggest an apparent reason to combine the disclosed elements.

This issue of obviousness with respect to combining known elements was addressed by the U.S. Supreme Court in *KSR Int'l Co. v. Teleflex Inc.*. 127 S.Ct. 1727 (2007). In their holding, the Court notably required a "flexible approach" to the application of the "teaching-suggestion-motivation" test when making an obviousness determination. *Id* at 1741. In allowing this more flexible approach, however, the Court did not abandon its long standing precedent that an invention "composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." *Id*. Under *KSR*, a determination of obviousness still requires an explicit statement of the reason a person of ordinary skill in the relevant field would be prompted "to combine the [prior art] elements in the way the claimed new invention does." *Id*. In other words, a determination of obviousness requires one to evaluate whether there is "an apparent reason to combine the known elements in the fashion claimed." *Id.*

Applicants have demonstrated in the specification and in the prosecution history that QS21 in simple solution is not well tolerated, causing severe necrosis at the injection site. *See*

U.S. Patent Pub. 2001/0053365 Page 7 at paragraphs 72-75 and Applicants' Response September 8, 2008 page 5 second full paragraph and attachment. The strong reactogenicity of QS21 disclosed by the Applicants would likely preclude its use as a vaccine adjuvant, but for Applicants' teaching of how the reactogencity of QS21 can be reduced while its adjuvant activity is maintained.

At the time of invention, the severe necrosis caused by QS21 at the injection site was unrecognized in the prior art generally, and in the references cited by the Examiner specifically. Kensil failed to observe the severe reactogenicity of QS21 disclosed by the Applicants and instead reported that QS21 was well tolerated when injected in mice. Column 27 lines 11-17. Lipford provided no guidance or teachings with respect to the reactogenicity of the disclosed liposomal compositions. One of ordinary skill in the art reading Kensil would be motivated to use QS21 *per se* as an adjuvant, since Kensil indicates that QS21 is well tolerated and it is generally advantageous to keep adjuvant formulations as simple as possible. Therefore the skilled person wanting to use QS21 as an adjuvant would simply take the teachings of Kensil without further modification or combination with other references. The present inventors realized that QS21 alone was not suitable for adjuvant use due to reactogenicity, and solved the problem by combining it with cholesterol in the claimed ratios. Lipford provides no teaching, suggestion or motivation in this regard - it does not mention toxicity of saponins, and makes no

reference to the fact that cholesterol may be used to address the issue of necrosis at the injection site.

Since neither reference recognizes the problem of necrosis at the injection site or discusses how to address it, without the use of hindsight, there is no apparent reason, that one of ordinary skill in the art would have been motivated to combine the elements of these references "in the way the claimed new invention does." *KSR* 127 S.Ct. at 1741.

As explained above, the Examiner has relied on the disclosure in the Kensil reference to provide the basis or reason for the motivation to use QS21 as a substitute for Quil A because, according to the Examiner, Kensil teaches:

(1) QS21 has adjuvant effect equal to or greater than Quil A.

(2) purified saponins show adjuvant effects at lower doses than crude saponins, and

(3) purified saponins are less toxic (hemolytic) than Quil A.

Applicants submit that the Examiner's reasoning is not supported by the Examiner's references to the Kensil disclosure, statements (1)-(3). During prosecution, Applicants challenged the accuracy of statement (1) above which says "QS21 has an adjuvant effect equal to or greater than Quil A," pointing out that the Kensil reference provides no direct comparison between the adjuvant effect of Quil A and QS21. See Applicants' Response February 9, 2006 page 7 second full paragraph. Kensil's teaching do not support the Examiner's conclusion with respect to statement (1).

Applicants also questioned whether statements (2) and (3) concerning "purified saponins" generally would inform one of skill in the art as to the characteristics of QS21 sufficiently to conclude that QS21 is an obvious substitute for Quil A. *Id.* at third full paragraph. Applicants maintain that the generalized statements regarding "purified saponins" could not inform one of skill in the art sufficiently to motivate the use of QS21 as a substitute for Quil A, primarily because the data in Kensil show that the purified saponins have widely varying characteristics. Statement (3) for example, while possibly accurate as applied to some of Kensil's purified saponins, is only partially accurate as applied to QS21. See Kensil Fig 12 and column 20 lines 36-39 (stating Quil A and QS21 "both caused partial hemolysis at concentrations as low as 25ug/ml"). Statements (2) and (3) do not support the Examiner's proposition that QS21 is an obvious substitute for Quil A.

The art does not teach or suggest an apparent reason to combine QS21 and cholesterol in the claimed ratio, giving the resulting composition with its unexpected and advantageous reductions in reactogenicity and preventing necrosis at the injection site. See Applicants Response of September 8, 2008. To conclude that the ratio is obvious in light of prior art is only possible with the aid of impermissible hindsight.

B. There is no motivation to combine the elements in the fashion claimed.

Even assuming *arguendo* the Examiner's combination of the elements from Lipford and

Kensil is supported, the combination does not render the claims obvious, as there is no motivation in the art to "combine the elements in the claimed fashion," that is, in the range of ratio's shown to reduce QS21 reactogenicity (above 1:1 to 1:100 or preferably above 1:1 to about 1:5). Applicants have argued that both Lipford and Kensil are silent with respect to the importance of the ratio between saponin and sterol. Lipford does not discuss the ratio of cholesterol to saponin. Kensil does not teach or suggest the use of cholesterol in combination with purified saponins. Neither reference discloses or suggests the claimed ratio of QS21 to cholesterol.

While Lipford does not explicitly suggest a QS21 to cholesterol ratio, Lipford does disclose a composition of Quil A and cholesterol. Using the Lipford disclosure one can calculate the ratio of Quil A to cholesterol in the Lipford composition to be 1:12.5. *See* August 10, 2005 Office Action, page 4 first full paragraph. Kensil teaches QS21 makes up approximately 3.7% of Quil A. Kensil column 13 Table 1. Thus, the ratio of unpurified QS21 to cholesterol disclosed in Lipford is 1:337, well outside the range of Applicants' claims. Applicants' Response, June 22, 2006 pages 5 and 6. Yet the Examiner rejects the Applicants' claimed ratios as obvious in light of the references because, the Examiner argues, "those of ordinary skill in the art would be motivated to use the same ratio of QS21 to sterol they would have used for Quil A to sterol." Office Action July 17, 2006 page 3 first full paragraph.

Applicants respectfully submit that the Examiner's rejection is not well taken. As stated

above, the Examiner supports the obviousness of substituting QS21 for the Quil A in the Lipford composition using the statements:

(1) QS21 has equal or greater adjuvant effect than Quil A,

(2) that purified saponins adjuvant effects at lower doses than crude saponins, and

(3) purified saponins are less toxic (hemolytic) than Quil A.

However, these statements do not support to the Examiner's conclusion that one of skill in the art would be motivated to directly substitute QS21 for Quil A (i.e. use the same ratio) in a Lipford-like composition .

Statements (1) and (2) undermine the Examiners conclusion that one of ordinary skill would be motivated to use the same amount of QS21 as Quil A in a "QS21-substituted" Lipford composition. Assuming for the sake of argument that QS21 can have a "greater adjuvant effect" than Quil A (statement 1), one of skill in the art would not be motivated to use the same amount of QS21 as Quil A in a Lipford composition. One of ordinary skill would be motivated to take into account the potentially greater adjuvant effect of QS21. This is especially true in light of Kensil's teaching that QS21 shows adjuvant effects at lower doses than Quil A (statement 2). Assuming statements 1 and 2 are accurate, Applicants submit that one of skill in the art would be motivated to substitute less QS21 for Quil A to account for the potency and the potentially "greater adjuvant effect" of QS21.

The Examiner further argues that one of ordinary skill in the art would not alter the

amount of cholesterol in a Lipford composition when substituting Quil A with QS21, but instead would be motivated to use the same saponin/sterol ratio shown in the original Lipford composition. In the 17 July 2006 Office Action, the Examiner explains that though the Kensil discloses "a reduced quantity of QS21 is required for adjuvant activity," the Examiner observes "there is no corresponding teaching suggesting the use of a reduced ratio of the sterol component relative to the saponin used." *Id*. (emphasis ours). Again, this argument runs contrary to Examiner's supporting statement from Kensil that "purified saponins are less toxic (hemolytic) than Quil A" (statement 3). Additionally, Applicants point out that a lack of a teaching to alter an unrecognized ratio does not equate to a suggestion to maintain it. Rather, the absence of any teaching relating to the saponin/sterol ratio serves, in this case, to reinforce Applicants' point, that there is no acknowledgement in the art of the significance of the saponin/sterol ratio and its effect on the reactogenicity of purified QS21.

II Ground for Rejection: Claim 95 is rejected by the Examiner under 35 U.S.C. §103(a) as being unpatentable over Lipford (Vaccine 12:72-80) in view of the teachings of Kensil (5,583,112) combined with routine optimization.

A. It is not obvious to optimize a result-effective parameter unrecognized in the art.

Claim 95 contains a preferred ratio of QS21 to sterol (from above 1:1 to about 1:5) which is not disclosed in the art, but which the Examiner states would be obvious through routine

optimization. Office Action March 9, 2007 page 4 first full paragraph. Applicants maintain this reduced ratio is not disclosed or suggested in the art.

As was explained above, in order to support the argument that one of ordinary skill in the art would maintain the cholesterol/saponin ratio of the Lipford composition when substituting QS21 for Quil A, the Examiner stated there was no "teaching suggesting the use of a reduced ratio of the sterol component relative to the saponin used." However, in the December 22, 2007 Advisory Action, "the Examiner rejected claim 95 giving the following explanation for why one would be motivated to alter the ratio as part of routine optimization. First, "QS21 has a somewhat reduced hemolytic activity compared to Quil A," and second, "Lipford indicates that the hemolytic activity of saponins appear to be due at least in part, to its ability to intercalate with cholesterol containing membranes." *Id*. Taken together these two teachings, according to the Examiner "[suggest to] a person of ordinary skill in the art that the presence of the cholesterol in ISCOMS may at least partially [be] responsible for the reduced hemolytic activity of the saponin in the ISCOM formulation." With this suggestion in mind, the Examiner then concludes "it would be obvious to those of ordinary skill in the art to vary the amount of cholesterol in ISCOMs to determine the optimal concentration of sterols required to minimize the hemolytic activity of the saponin." *Id*. emphasis ours.

Initially, Applicants point out that the claims are not drawn to an optimized cholesterol/saponin ratio that reduces hemolytic activity in an ISCOM containing Quil A. Even

assuming the Examiner was correct in his conclusion that it would be obvious to vary the amount of cholesterol in an ISCOM to optimize the concentration of sterols and thereby minimize the hemolytic activity of Quil A, the Examiner has not shown, and it does not follow, that based on observations regarding Quil A in ISCOMS, it would be obvious to optimize cholesterol concentrations in non-ISCOM formulations using QS21. This is especially true since QS21 was thought to be incompatible with ISCOM formation and has a different hemolytic activity than Quil A. See Applicants' Response February 9, 2006 pages 6 and 7.

The Examiner stated that claim 95 is "rejected as obvious by routine optimization of the ratios of the components in an adjuvant composition." Office Action March 9, 2007 page 4 first full paragraph. Case law holds that when a parameter to be optimized is not recognized in the prior art as one that affects the results, optimization of the parameter is not per se obvious. *In re Antonie*. 559 F.2d 618, 620 (CCPA 1977). In the case of *In re Antonie*, Applicants devised and claimed a waste treatment system with a specific "tank volume" to "contractor area" ratio and disclosed the ratio as having a beneficial effect on treatment capacity. Even though the tank volume and contractor area of a waste treatment system were known parameters, there was no teaching in the art that a particular ratio of tank volume to contractor area would produce the advantageous effect. Therefore, the court held it could not be obvious to optimize the ratio in the manner claimed. *Id.* See also MPEP 2144.05.IIB Optimization of Ranges-Only Result Effective Variables can be Optimized.

In re Antonie was also recently relied upon in a precedential opinion by the BPAI, *Ex parte Whalen II*. Appeal 2007-4423 (2008). In *Ex parte Whalen II*, the Applicants invented an embolic composition with an increased viscosity over prior art compositions that provided a beneficial effect. *Id* at pages 2 and 3. The viscosity of prior art embolic compositions was known, but nothing in the art suggested increasing the viscosity of embolic compositions in the manner claimed to provide the advantageous benefit disclosed by the Applicants. *Id* at page 14. The Board held that routine optimization of the viscosity would not render the claim obvious and suggested that the prior art actually lead away from the claimed increase in viscosity. *Id* at page 15.

With respect to Applicants' claims, the prior art discloses a ratio of QS21 to sterol in Lipford's composition, but as in *In re Antonie*, the art does not recognize the effect of the ratio of purified QS21 to cholesterol on the reactogenicity of the composition. There is no suggestion that it reduces the severe necrosis observed at the injection site of QS21 compositions. Likewise, there is nothing in the cited references that would suggest altering or optimizing the unrecognized ratio in such a way as to arrive at the Applicants' claimed ratio, as was the case in *Ex parte Whalen II*.

SUMMARY

Applicants submit that (i) the cited art does not support the Examiner's reasoning for

combining the disclosed elements and (ii) there is no motivation to combine the elements in the fashion claimed. Applicants request the Board reverse the rejection of claims 74-76, 78, 80, 82-84, 94 and 95 under U.S.C. §103(a) as being unpatentable over Lipford (Vaccine 12:72-80) in view of the teachings of Kensil (U.S. 5,583,112) and the rejection of claims 77, 79 and 81 under 35 U.S.C. §103(a) as being unpatentable over Lipford (Vaccine 12:72-80) in view of the teachings of Kensil (5,583,112) and further in view of Prieels et al (WO94/00153).

Applicants also maintain that even if the cited art can be combined, it would not be obvious to one of skill in the art to optimize the QS21/cholesterol ratio as claimed by applicants in claim 95, since the ratio was not recognized in the prior art as one that affects the results. Applicants request the Board reverse the rejection of claim 95 under 35 U.S.C. §103 as being unpatentable over Lipford (Vaccine 12:72-80) in view of the teachings of Kensil (U.S 5,583,112), by routine optimization.

Respectfully submitted,

/Michael M. Conger/
Michael M. Conger
Registration No. 43,562

CLAIMS APPENDIX

1-73. (Canceled)

74. (Previously presented) A composition comprising: 1) an antigen; 2) a saponin which is substantially pure QS21; 3) a sterol that is present in excess by weight with respect to the saponin and wherein the ratio of saponin to sterol does not exceed 1:100 w/w.

75. (Previously presented) The composition of Claim 74 wherein the weight:weight ratio of QS21 to sterol is 1:2 to 1:100.

76. (Previously presented) The composition of Claim 75 wherein the sterol is cholesterol.

77. (Previously presented) The composition of Claim 74 which further comprises a derivative of an enterobacterial lipopolysaccharide.

78. (Previously presented) The composition of Claim 74 which further comprises a metal particle salt carrier selected from the group consisting of phosphate and hydroxide salts of aluminum, zinc, calcium, cerium, chromium, iron, and beryllium.

79. (Previously presented) The composition of Claim 76 which further comprises a 3-O-deacylated monophosphoryl lipid A.

80. (Previously presented) The composition of Claim 76 which further comprises aluminum hydroxide or aluminum phosphate.

81. (Previously presented) The composition of Claim 76 which further comprises a 3-O-deacylated monophosphoryl lipid A and aluminum hydroxide or aluminum phosphate.

82 (Previously presented) The composition of Claim 79 wherein the saponin is at least 98% pure QS21.

83. (Previously presented) The composition of Claim 74 wherein the sterol and the QS21 are in a vesicle-like structure.

84. (Previously presented) The composition of Claim 74 wherein the antigen is derived from Human Immunodeficiency virus, Feline Immunodeficiency virus, Varicella Zoster virus, Herpes Simplex virus type 1, Herpes Simplex virus type 2, Human cytomegalovirus, Hepatitis A, Hepatitis B, Hepatitis C, Hepatitis E, Respiratory Syncytial virus, Human Papilloma virus, Influenza virus, Haemophilus Influenza B, Meningitis virus, Salmonella, Neisseria, Borrelia, Chlamydia, Bordetella, Plasmodium, or Toxoplasma.

85-93 (Canceled)

94. (Previously presented) The composition of 83 wherein the sterol is cholesterol and the vesicle like structures are unilamellar liposomes.

95. (Previously presented) The composition of claim 74 wherein the ratio of saponin to sterol is between above 1:1 and about 1:5 w/w.

EVIDENCE APPENDIX

Not applicable

RELATED PROCEEDINGS APPENDIX

Not applicable